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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,298	02/08/2000	JUNKO YAMAMOTO	1422-411P	1749

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,298	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21,27,28,30,44,46,50 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,27,28,30,44,46,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on May 26, 2006.

Preliminary Remark

Claims 1-19, 22-26, 29, 31-43, 45, and 47-49 have been canceled.

Claims 50 and 51 are newly submitted.

Claims 20, 21, 27, 28, 30, 44, 46, 50, and 51 are pending and are under prosecution herein

Claim Rejections - 35 USC § 112 – Necessitated by Amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

Claim 50 recites that the polymerase chain reaction is carried out by a setting a denaturation temperature of between approximately 80°C and 85°C. Claim 50 depends from claim 21 which recites that the method involves RT-PCR involving the recited combination of nucleotide analogs.

The specification provides for proper written support for the claimed range of PCR amplification reaction (i.e., between 80°C and 85°C), when employed in conjunction with formamide having a final concentration of 1% by weight to 20% weight. (see page 17, lines 21-25, Specification).

The specification does not have proper written support for a method which does not involve the use of the requisite amount of formamide and the specification does not provide any support for a range which is between approximately 80°C and 85°C).

Claim 51 recites that the polymerase chain reaction is carried out by a setting a denaturation temperature of between approximately 80°C and 85°C. Claim 51 depends from claim 28 which recites that the method involves RT-PCR involving the recited combination of nucleotide analogs and any compound that lowers the Tm value of a double-stranded nucleic acid.

The specification provides for proper written support for the claimed range of PCR amplification reaction (i.e., between 80°C and 85°C), when employed in conjunction with single species of compound which lowers the Tm of a double-stranded nucleic acid, which is formamide having a final concentration of 1% by weight to 20% weight. (see page 17, lines 21-25, Specification).

The specification does not have proper written support for a method which contemplates the claimed range of melting temperature for a broader breadth of compounds which are responsible for lowering Tm of a double-stranded nucleic acid and the specification does not provide any support for a range which is between approximately 80°C and 85°C).

Removal of new matter is required.

Claim Rejections - 35 USC § 103

The rejection of claims 20, 21, and 44 under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (U.S. Patent No. 5,693,517) in view of Kaiser et al. (U.S. Patent No. 5,843,669) made in the Office Action mailed on February 28, 2006 is withdrawn in view of the Amendment received

on May 26, 2006, amending the clams to require the reverse transcription reaction to be conducted via use of 7-Deaza-dATP and at least one of 7-Deaza-dGTP or dITP.

The rejection of claims 23, 24, 26, and 45 under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (U.S. Patent No. 5,693,517) in view of Kaiser et al. (U.S. Patent No. 5,843,669) and Pergolizzi et al. (U.S. Patent No. 5,658,764), made in the Office Action mailed on February 28, 2006 is withdrawn in view of the Amendment received on May 26, 2006, canceling the rejected claims.

The rejection of claims 27, 28, 30, and 46 under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (U.S. Patent No. 5,693,517) in view of Kaiser et al. (U.S. Patent No. 5,843,669) and Pergolizzi et al. (U.S. Patent No. 5,658,764), made in the Office Action mailed on February 28, 2006 is withdrawn in view of the Amendment received on May 26, 2006 amending the clams to require the reverse transcription reaction to be conducted via use of 7-Deaza-dATP and at least one of 7-Deaza-dGTP or dITP.

Rejections, New Grounds – Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 21, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bauer et al. (Nucleic Acids Research, 1990, vol. 18, no. 4) in view of Kaiser et al. (U.S. Patent No. 5,843,669).

Bauer et al. disclose method of performing reverse transcription reaction involving 7-Deaza-dATP and 7-Deaza-dGTP (*see* page 880, 2nd column, 5th paragraph, 6th-7th line).

Bauer et al. do not teach a PCR reaction employing the same set of reagents.

Kaiser et al. disclose a method of amplifying (via PCR) employing 7-Deaza-dATP and 7-Deaza-dGTP) (column 24, lines 29-26; column 183, lines 1-9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bauer et al. and Kaiser et al., thereby arriving at the claimed invention for the following reasons.

The technique of RT-PCR is a well-known process of amplifying a sample in a species, wherein the target nucleic acid to be amplified is an RNA or mRNA.

Bauer et al. recognizes the problems associated with reverse transcribing RNAs, wherein the use of naturally occurring nucleotide analogs results in, "[p]remature chain terminations [which] are caused by secondary structures or by modified nucleotides within the RNA template..." (page 879, 1st column, 3rd paragraph).

The artisans seeks to overcome such a problem by the use of nucleotide analogs, 7-Deaza-dATP and 7-Deaza-dGTP (page 880, 2nd column, bottom paragraph), wherein the artisans expressly disclose that, "[t]he use of c^7-deaza analogs of dATP and dGTP ***depress band compressions*** to a very large extent..." (page 884, 1st column, 1st paragraph) which is disclosed as being largely responsible for, "***complete termination of reverse transcription***" due to the template's "rigid structure" (page 884, 1st column, 1st paragraph).

With regard to the combination of the teachings of Bauer et al. with that of Kaiser et al., Kaiser expresses the same motivation for employing the modified nucleotides in their PCR reaction:

"The 7-deaza purine analogs (7-deaza-dATP and 7-deaza-dGTP) serve to ***destabilize regions of secondary structure by weakening the intrastrand stacking of multiple adjacent purines. This effect can allow amplification of nucleic acids that, with the use of natural dNTPs, are resistant to amplification because of strong secondary structure***" (column 183, lines 1-8).

Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the RT reaction of Bauer et al. and the PCR reaction Kaiser et al. (RT-PCR reaction) for the same benefit of reverse transcribing/amplifying a nucleic acid sequence with the same set of 7-deaza nucleotide analogs, for the same expressly stated advantage of reverse-transcribe and amplify target nucleic acids having a strong secondary structure.

Since both of the artisans employ the same set of modified nucleotide analogs for the same advantage, one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at combining the teachings of Bauer et al. with the teachings of Kaiser et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 27, 28, 30, 46, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bauer et al. (Nucleic Acids Research, 1990, vol. 18, no. 4) in view of Kaiser et al. (U.S. Patent No. 5,843,669, issued December 1, 1998, filed November 29, 1996) and Pergolizzi et al. (U.S. Patent No. 5,658,764, issued August 19, 1997).

Bauer et al. disclose method of performing reverse transcription reaction involving 7-Deaza-dATP and 7-Deaza-dGTP (*see* page 880, 2nd column, 5th paragraph, 6th-7th line).

Bauer et al. do not teach a PCR reaction employing the same set of reagents.

Bauer et al. do not teach said PCR reaction involving compounds which lower the melting temperature of double-stranded nucleic acid.

Kaiser et al. disclose a method of amplifying (via PCR) employing 7-Deaza-dATP and 7-Deaza-dGTP) (column 24, lines 29-26; column 183, lines 1-9).

Perfolizzi et al. disclose a method of amplifying a target nucleic acid by a polymerase chain reaction (PCR), wherein the reaction employs nucleoside analog 7-deaza dGTP as well as DMSO (dimethyl sulfoxide) (see column 8, lines 43-52).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bauer et al., Kaiser et al., and Perfolizzi et al., thereby arriving at the claimed invention for the following reasons.

The technique of RT-PCR is a well-known process of amplifying a sample in a species, wherein the target nucleic acid to be amplified is an RNA or mRNA.

Bauer et al. recognizes the problems associated with reverse transcribing RNAs, wherein the use of naturally occurring nucleotide analogs results in, "[p]remature chain terminations [which] are caused by secondary structures or by modified nucleotides within the RNA template..." (page 879, 1st column, 3rd paragraph).

The artisans seeks to overcome such a problem by the use of nucleotide analogs, 7-Deaza-dATP and 7-Deaza-dGTP (page 880, 2nd column, bottom paragraph), wherein the artisans expressly disclose that, "[t]he use of c^7-deaza analogs of dATP and dGTP ***depress band compressions*** to a very large extent..." (page 884, 1st column, 1st paragraph) which is disclosed as being largely responsible for, "***complete termination of reverse transcription***" due to the template's "rigid structure" (page 884, 1st column, 1st paragraph).

With regard to the combination of the teachings of Bauer et al. with that of Kaiser et al., Kaiser expresses the same motivation for employing the modified nucleotides in their PCR reaction:

> "The 7-deaza purine analogs (7-deaza-dATP and 7-deaza-dGTP) serve to ***destabilize regions of secondary structure by weakening the intrastrand stacking of multiple adjacent purines. This effect can allow amplification of nucleic acids that, with the use of natural dNTPs, are resistant to amplification because of strong secondary structure***" (column 183, lines 1-8).

Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the RT reaction of Bauer et al. and the PCR reaction Kaiser et al. (RT-PCR reaction) for the same benefit of reverse transcribing/amplifying a nucleic acid sequence with the same set of 7-deaza nucleotide analogs, for the same expressly stated advantage of reverse-transcribe and amplify target nucleic acids having a strong secondary structure.

Since both of the artisans employ the same set of modified nucleotide analogs for the same advantage, one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at combining the teachings of Bauer et al. with the teachings of Kaiser et al.

Finally, the motivation to combine a compound which lowers the Tm temperature of a double stranded nucleic acid during PCR reaction, is explicitly provided for by Pergolizzi et al.:

> "The inability of PCR-based methods to detect GC-rich sequence has hindered the development of an assay for other conditions." (column 3, lines 1-3)

Such difficulty, as recognized in the art, arises from the strong hydrogen bonds formed between the base, "G: and its complementary base "C" in the GC rich region.

Pergolizzi et al., in their attempt to overcome this difficulty, disclose a method which employs reagents which render the double-strand nucleic acid, single stranded for amplification.

Pergolizzi et al. explicitly disclose a preferred embodiment employing 7-deaza GTP and 10% DMSO in an amplification reaction.

Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the reagents of Pergolizzi et al. with the teachings of Bauer et al. and Kaiser et al. for the advantage of facilitating melting (*i.e.,* become single stranded) of any double stranded nucleic acids, such as DMSO, in an amplification reaction.

As Pergolizzi et al. already couples 7-deaza GTP with DMSO in a PCR reaction, one of ordinary skill in the art would have had a clear expectation of success at combining the PCR reaction of Pergolizzi et al. with the teachings of Bauer et al. and Kaiser et al.

With regard to the determination of the optimal conditions for conducting the PCR reaction involving the modified nucleotide analogs, such would involve routine optimization of one of ordinary skill in the art in the discipline of nucleic acid amplification. Given the fact that the artisans endeavor to employ nucleotide analogs so as to facilitating melting of the template nucleic acids, actual determination of such temperature would have been well-within the purview of an ordinarily skilled artisan involving routine experimentation to arrive at an optimal condition.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Applicant's arguments with respect to rejections of record have been considered but are moot in view of the new ground(s) of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent

to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
8/1/2006

YOUNG J. KIM
PRIMARY EXAMINER

YJK